Trends-in-Medicine

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SUMMARY

U.S. cardiologists are not particularly concerned about late stent thrombosis, durable polymers, or the need for Sanofi-Aventis' Plavix with drug-eluting stents, and they see little difference between Cypher and Taxus in those regards. ♦ Among doctors at CRT, use of Johnson & Johnson's Cypher and Boston Scientific's Taxus is fairly evenly split and likely to remain that way for the rest of this year. ♦ The FDA is taking a very cautious approach to PFO closure, and agency officials said bioabsorbable stents face formidable challenges. ♦ A company to watch: CardioMind.

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CARDIOVASCULAR REVASCULARIZATION THERAPIES (CRT)

Washington, DC
March 28-30, 2006

CRT, sponsored by the Cardiovascular Research Institute at Washington Hospital Center, is a much smaller meeting than TCT, but it is a good opportunity to talk with opinion leaders and regulatory officials. There were little new data at CRT, but the *Workshops with the FDA* provided some insight into the regulatory hurdles that PFO closure, bioabsorbable stents, and percutaneous valves face.

DRUG-ELUTING STENTS (DES)

Seventeen interventional cardiologists were asked about the outlook for drug-eluting stent use and safety issues. Sources agreed that the use of bare metal stents (BMS) is flat or decreasing. Most said that their use of BMS averages 5% of total stents.

- *New Hampshire:* "We use bare metal stents rarely – only about 4%-5% of the time. We use them in our cath lab for small lesions."
- *Pennsylvania #1:* "We use less than 5% BMS, most in patients with a 4.0 mm or greater vessel."
- *Ohio:* "I use it for 3.5 mm (vessel diameter) and above."
- *Pennsylvania #2:* "Use isn't increasing at all; it's decreasing."

U.S. cardiologists indicated that they are not particularly concerned about stent thrombosis or the safety of the drug-eluting stents, the durable polymers used on them, or about the potential need for extended use of Sanofi-Aventis' Plavix (clopidogrel) after a drug-eluting stent is implanted.

- *New Hampshire:* "No, drug-eluting stents are terrific, with restenosis rates of less than 10%. And it appears that you can give Plavix for nine months and then stop. So we're not concerned about the safety of the polymer, although, in the long run, it remains to be seen."
- *Washington DC #1:* "There aren't any safety issues."
- *Washington DC #2:* "There aren't any major safety issues, but we are still learning about the long-term effects."
- *Washington DC #3:* "This is actively being debated by all cardiologists. Most would say drug-eluting stents are safe, but it is not as simple as that."
- *North Carolina:* "Stent thrombosis is not on the radar screen of the average interventional cardiologist, but it is a potential issue…Late thrombosis occurs but not often."

- *Ohio:* "Most studies are sponsored by industry, and we won't really know until there are independent studies. There won't be any quick shift to a polymer-less stent, but that will be a marketing message. For me to shift stents takes more than a small number of patients (tested)."
- *Missouri:* "There aren't many safety concerns; decisions are based on size and length."

Dr. Renu Virmani of CVPath, International Registry of Pathology, Gaithersburg MD asked, "Is stent thrombosis a problem in drug-eluting stents?" She concluded it is. Asked if doctors are overzealous in the use of drug-eluting stents, she said, "I do think we're overzealous…I believe that if you take the best stent on the market, vessels greater than 2.8 mm showed no benefit with a drug-eluting stent, and it (the DES) may in fact be harmful. If that patient is taken off clopidogrel for whatever reason, you're likely to get a higher risk of thrombosis."

Doctors were asked to rank (on a scale of 1-10, with 10 the highest) the deliverability of Conor MedSystem's CoStar, Johnson & Johnson's Cypher, Medtronic's Endeavor, and Boston Scientific's Taxus Liberté (the newest Taxus stent, which is available in Europe now and is expected in the U.S. later this year – once Boston Scientific resolves its FDA manufacturing issues). A doctor commented, "Deliverability is really not that different for experienced cardiologists, but deliverability does matter to the grassroots guy." On average, they rated:

- Endeavor 8.5
- Taxus Liberté 8.25
- CoStar 7.5
- Cypher 5.25

Taxus vs. Cypher

Dr. Ron Waksman, the organizer of the CRT meeting, said that Taxus has proven slightly – but not significantly – safer than Cypher at the Washington Hospital Center.

Washington Hospital Center Drug-Eluting Stents Experience

Measurement	Cypher n=776	Taxus n=366
TLR	2.0	2.8
SAT	1.8	1.1
SAT in diabetics	2.0	1.5

Dr. Charles Simonton of the Sanger Clinic, Carolinas Heart Institute in Charlotte NC, compared the Taxus and Cypher stents using recent head-to-head trials and registry data. He said that the REALITY trial is the only trial powered enough to show any significant differences between the two drug-eluting stents, and that trial "showed no difference between Taxus and Cypher." He added, "We now have more than 5,000 patients worldwide, comparing these two stents in registries, including the STENT trial which showed no statistically significant difference between Cypher and Taxus ...There was no statistically significant difference in death, MI, TVR, or MACE." Asked about adding bare metal stents to the registry for comparison, he said, "I think bare metal might have a role in the larger vessels."

Sources were split on their use of the two FDA-approved drug-eluting stents: 56% Johnson & Johnson's Cypher and 44% Boston Scientific's Taxus, with no significant change in usage expected over the next year. Most sources insisted there isn't much difference between the two stents. Taxus fans cited its ease of delivery, while Cypher fans claimed they get slightly better results with that stent. Although sources predicted no change in usage over the next three to six months, one doctor said he would change his preferred stent (Taxus) if there were a price change of more than 10%. U.S. doctors were reluctant to predict the outlook for other drug-eluting stents on the horizon, and European doctors who already have some of these available (e.g., Conor's CoStar and Sorin's Janus) said usage is slowly increasing for some, but most are remaining niche products, at least for now.

- *New Hampshire:* "Taxus is slightly easier to deploy, and Cypher has a slightly lower stenosis rate. Both result in less than 10% restenosis."
- *Pennsylvania:* "We use Cypher exclusively – 100%. I have no real preference, although Taxus is better in tough situations."
- *Ohio:* "We use Cypher and Taxus 60%-40%, respectively. We get a little better results with Cypher."
- *North Carolina:* "Conor is not likely to cause a big shift in usage…If (Medtronic's) Endeavor is not-inferior in the ENDEAVOR-IV trial, it might still be approved by the FDA – if the stent thrombosis rate is low. The FDA is hungry for another drug-eluting stent."
- *Middle East:* "There is no real difference between Cypher and Taxus, so there is no reason to change, but Conor could get 30%-40% (share) if it were priced 10% below the Taxus because deliverability is the issue."
- *Iowa:* "Taxus is the most deliverable stent, and that's why we use it more than Cypher."

Overlapping Taxus vs. bare Express stents

A poster reported on a comparison of these two stents in swine, indicating there is healing over time with Taxus. The researchers concluded: There is equivalent endothelial cell coverage between Taxus and a bare Express stent, beginning at two days and nearly complete at 20 days. There is endothelialized neointima at 20 days, and "the presence of multinucleated giant cells with both suggests a previously unknown mechanism for early strut coverage."

Porcine Healing Study

Time period	>90% coverage		75%-90% coverage	
	Taxus	Express	Taxus	Express
Day 2	0	0	0	0
Day 4	47%	52%	43%	44%
Day 10	82%	97%	15%	3%
Day 20	100%	100%	---	---
Multinucleated giant cells				
Day 4	Large areas of struts covered			
Day 10	Largely disappeared			

ABBOTT

A poster presented the results in swine with Abbot's follow-up drug-eluting stent using a combination of dexamethasone and zotarolimus (ABT-578) vs. a bare TriMaxx vs. the zotarolimus-eluting ZoMaxx. The drug combination showed more decrease in neointima than ZoMaxx alone "indicating a clear improvement in the efficacy of (vs.) zotarolimus alone."

Combination Dexamethasone + Zotarolimus

Measurement	TriMaxx n=9	ZoMaxx n=24	Dexamethasone + zotarolimus n=24
Neointimal area	~2.4 mm^2	~1.6 mm^2	~1.3 mm^2 (Down 49% vs. TriMaxx, p=.003)
Injury score	N/A	0.26	0.15 (Nss vs. ZoMaxx)

Bifurcations

Dr. Maurice Buchbinder of Scripps Medical Center in California said that the advent of drug-eluting stents "hasn't solved the problem of bifurcation." He said the four major techniques for bifurcation disease are elective T-stenting, provisional T-stenting, crush stenting, and V-stenting, adding that he hates crush stenting.

The most common technique is side branch ostium scaffolding. He said, "One stent takes care of the main branch, leaving the side branch to be reassessed following stenting. But when you try to dilate the side branch, you pull back some of the main branch, and you are not covering the vessel the way you should be…even with the kissing balloon." However, he said that procedure success has been very high and in-hospital complications are very low, but there has been a very wide range of restenosis, from 26%-62%. He said the quest is to find something that:

- Is easy to implant and guarantees a high rate of technical success.
- Has the capacity for rotation in order to fit the coronary anatomy in a 3-D model.
- Allows continuous access to both branches.
- Offers optimal scaffolding.

One of the most promising dedicated bifurcation stents is **Boston Scientific's Petal** stent, which has a side branch stent that pops up as it is inflated. The stent system has a big balloon and a small balloon, which pushes the Petal stent into the side branch. Dr. Waksman said, "This Petal can be placed in any stent that is available, so it is an add-on feature. Boston Scientific has the rights for this stent, and it will be coming out in the next year and a half…It is extremely flexible, even at a 90 degree angle. The problem, unfortunately, is that restenosis is a problem, despite the procedural outcome and improvement. Early human experience with the Petal stent appears very promising, but clearly the drug-eluting stent version will be coming in the next few months."

BIOSENSORS' BioMatrix

The BEACON registry in S.E. Asia and India of the BioMatrix is an ongoing, all-comers study. As of February 17, 2006, 443 patients with 668 stents had been enrolled. The primary endpoint is TVR at 6 months; the secondary endpoint is MACE at 1, 3, 6, and 12 months.

Preliminary Results of the BEACON Registry

Measurement	BioMatrix
>1 stent	58%
Post-procedure MLD	2.93 mm (102% of pre-procedure MLD of 2.87 mm)
Average lesion length	18.3 mm
30-day results	
TVR	0
MACE	2.75%
Death	0.25%
Q-wave MI	0.5%
Non-Q-wave MI	2.5%
CABG	0
TLR	0
TVR	0

Chronic total occlusions (CTO)

In a poster, researchers reported on a multicenter, prospective European study of FlowCardia's Crosser, a monorail catheter platform, in 97 CTOs in 94 patients. They found that the Crosser system was well-tolerated in all patients, and there were no procedural complications or clinical perforations. The results showed the Crosser is safe and effectively

Crosser European Trial

Measurement	Crosser
Original platform (n=97 CTOs in 94 patients)	
Technical success	58.8% of vessels
Overall success	57.7%
Average occlusion length	22 mm
Average activation time	2 min. 49 secs.
Revised platform (n=67 CTOs in 64 patients)	
Success rate	64.2%

recanalizes CTOs with a high clinical success rate. Device improvements were made following the feasibility study, and the improved Crosser platform achieved a higher success rate. The researchers concluded that Crosser appears to be safe, clinically efficient, and complementary to conventional guidewire manipulation. They predicted it has a good potential for CTO treatment, but said additional trials are needed to prove efficacy on a large scale.

At a session, Dr. John Laird of the Washington Hospital Center commented, "An interesting technique now getting into trials is FlowCardia's Crosser catheter, which is being studied in an ongoing PATRIOT trial…Using ultrasound technology, it allows us to more easily cross difficult occlusions. We've had a couple of occasions that were very promising, and we'll see how this pans out over time."

The biggest area of interest with regard to peripheral CTOs is re-entry devices, according to Dr. Laird. He suggested two other catheters are of interest: LuMend/Johnson & Johnson's Outback catheter and Medtronic's Pioneer catheter. He said, "We find the Pioneer catheter particularly useful for chronic iliac occlusions…So the standard approach most likely would be hydrophobic guidewire with a support catheter. In some places, the preferred application would be to advance the guidewire and pop it through distally and then balloon dilate and stent the occlusion. If you fail, then try some of the alternative technologies, such as the (LuMend) Frontrunner catheter, (Intraluminal Therapeutics') Safe-Cross wire, the FlowCardia device, etc."

Dr. Patrick Whitlow of the Cleveland Clinic described LuMend's Outback LTD re-entry catheter, which uses a side port cannula needle exit, with the cannula needle keyed to the catheter shaft, using a more consistent needle path. He said, "It's called LTD because you locate the false lumen and face the L shape toward the true lumen." He said that the coronary device was bought by Johnson & Johnson/Cordis, advising, "If you have some on the shelf, you can use them, but it will be discontinued. That's why we're using the SFA device for long, calcified occlusions or proximal occlusions where it is hard to get the wire through. (J&J) Cordis is very distracted by not having any R&D for four years. I think it will come back in three to four years, but right now there simply aren't the resources to make it work."

Dr. Simonton said, "We should be opening these CTOs. The most common cause of failed recanalization is the inability to cross with a wire – either you can't find an entry point or you can't re-enter." He described other new devices for CTO recanalization, including:

- **Guidewires:** Abbott/Guidant's Cross-It XT and Asahi Intec's Miracle Brothers.
- **Ablative:** Spectranetics' excimer laser wire and FlowCardia's ultrasound.
- **RF ablation:** Intraluminal Therapeutics' Safe-Cross RF.
- **Mechanical:** LuMend's Frontrunner and Intraluminal Therapeutics' Safe-Cross AP.

Drug-eluting stents for saphenous vein graft (SVG) intervention

A poster reported on a Washington Hospital Center study comparing the efficacy of Cypher vs. Taxus for saphenous vein grafts in 89 patients (47 who got Cypher and 42 who got Taxus). The researchers concluded that the use of DES in patients:

- Undergoing SVG intervention with a distal protection device is clinically safe and feasible.
- Cypher and Taxus have the same efficacy and clinical outcome in SVG interventions out to six months.
- Large randomized studies using drug-eluting stents in larger sizes and with longer follow-up are needed.

Novel Stents and Stent-Related Products

CardioMind

This private company, founded by Julian Nikolchev, a biomechanical engineer, has an ultra low-profile stent system for coronary and peripheral artery disease in development. The self-expanding, balloon-less stent is "hidden inside the (0.14 mm) guidewire." It is designed for use in complex lesions that traditionally-sized stent delivery technologies have difficulty reaching – vessels <3.0 mm and tortuous vessels. Reportedly, it has the thinnest stent struts yet. The company isn't pursuing neurological applications yet, but it is said to be considering that for the future.

Doctors were fairly excited about this stent-in-a-wire product. It hasn't gotten a lot of publicity, and the company insists it doesn't really want to raise its profile yet, but key interventional cardiologists are watching it closely. At the time of CRT, it was in preclinical development, but human clinical trials were expected to start later this year, initially with a bare metal stent, but a drug-eluting stent (with a ′limus but perhaps no polymer) is planned. The advantage, an expert said, is the crossing profile.

CV Therapeutics' PLLA Coating

CV Therapeutics is working on a PLLA stent polymer, and an expert, noting that not all PLLAs are the same, said it looks very promising.

Disa Vascular's paclitaxel-eluting stent with a bioabsorbable polymer

In a poster, researchers at St. Joseph's Hospital in Atlanta and in South Africa evaluated a second generation drug-eluting stent by this South African company, which is comprised of a bioabsorbable polymer eluting a moderate dose of paclitaxel

in a clinically relevant porcine coronary artery model. They concluded:

- Despite *in-vitro* data showing slow, sustained release within the range of dosages and elution rates reported for other commercially available or investigational paclitaxel-eluting stents, *in-vivo* data demonstrated a time-dependent phenomenon of profound vessel wall toxicity, culminating in excessive neointimal formation for paclitaxel-eluting from a bioabsorbable polymer.
- Excessive local toxicity should be considered a marker for potential long-term adverse outcomes such as late restenosis.
- The window of safety and efficacy for paclitaxel may not be as broad as currently interpreted in the literature.

However, a source was dubious about this device's chances of success.

GENZYME/AVIGEN'S gene therapy for Parkinson's

Researchers from the University of California, Berkeley, reported on four patients undergoing gene therapy for Parkinson's Disease, and said they are about to start the fifth patient. The genes are delivered surgically with an adeno-associated virus carrier into the brain via catheter.

Parkinson's Gene Therapy

Measurement	Patients off medications	Patients on medications
Baseline UPDRS	69%	35%
Baseline UPDRS-III	41%	16%
UPDRS at 6 months	49%	24%
UPDRS-III at 6 months	27%	12%

Morphometric Parameters in Porcine Coronary Arteries

Measurement	1 month	3 months	6 months	12 months
Control				
Vessel area (mm^2)	6.38	6.61	7.16	6.32
Stent area (mm^2)	5.43	5.18	6.04	5.19
Lumen area (mm^2)	3.65	3.56	2.23	3.19
Medial area (mm^2)	0.97	1.42	1.12	1.13
Neointima area (mm^2)	1.77	1.84	2.81	1.99
% occlusion	29.86	37.52	46.25	38.71
Mean injury score	0.56	0.50	1.54	1.93
AMS				
Vessel area (mm^2)	4.05	4.28	3.83	4.56
Stent area (mm^2)	3.12	3.53	3.09	3.83
Lumen area (mm^2)	2.05	2.37	1.80	2.56
Medial area (mm^2)	0.94	0.76	0.74	0.73
Neointima area (mm^2)	1.05	1.16	1.48	1.27
% occlusion	33.38	35.05	46.67	35.75
Mean injury score	0.19	0.47	1.06	1.09

Magnesium alloy stents

Researchers at the MedStar Research Institute of Washington DC studied magnesium alloy stents in porcine coronary arteries and concluded, "Absorbable metal stents (AMS) carry the potential to overcome the limitations posed by permanent metallic stents, such as chronic inflammation, late stent thrombosis, and prolonged antiplatelet therapy. Furthermore, the physiological function of the vessels is restored after loss of structural integrity of the stent." The study tested the long-term safety and efficacy of AMS in pigs, finding that the AMS were completely absorbed. At all time points the neointimal formation in the AMS group was lower as compared to control. The stents appeared safe, with no evidence of thrombosis or inflammation and complete re-endothelialization at 12-month follow-up.

IMAGING

In a poster, researchers from the Cardiovascular Institute of the South in Louisiana reported on their look at 64-channel multidetector computed tomography angiography (MDCTA) in non-cardiac vascular disease. They concluded that 64-slice MDCTA is accurate in imaging the superficial femoral artery (SFA), infrapopliteal arteries, etc., with minor protocol changes. Therefore, the advantages of 64-channel high-resolution output are applicable to non-cardiovascular disease.

DRUGS

Asked about **The Medicine Company's** Angiomax (bivalirudin) and the results of the ACUITY trial which was presented at the American College of Cardiology meeting in March 2006, most sources said they use Angiomax in their cath lab – but not because of the ACUITY results. Comments included:

- *New Hampshire:* "We use it, and its use will increase, but not necessarily because of the ACUITY trial – because it works."
- *Pennsylvania:* "It depends on the doctor. In acute MI I don't use it, but in routine elective procedures, I will. Use will probably increase. I like it because of its half-life and because there is less bleeding."
- *Washington DC:* "In the ACUITY trial, Angiomax alone had no significant bleeding, so it is clinically equivalent (to heparin). But bivalirudin was associated with a big reduction in bleeding, and that did improve the long-term outcome."
- *Missouri:* "About 25% of our procedures are Angiomax. I think use would increase if the cost went down. Cost is the most important thing, especially at the VA hospital."
- *Iowa:* "We use Angiomax 100%. It hasn't gone to the ER because ACUITY didn't address that. We give it five hours before a procedure, and I don't call that upstream."

- *Pennsylvania:* "We use Angiomax, but not because of the ACUITY trial."
- *North Carolina:* "It will take a while for the message to get out, but it's one more strike against GP IIb/IIIas…It was a little of a mixed trial. If you want to promote upstream use, you need to do a trial like the big IIb/IIIa trials."
- *Virginia:* "That (ACUITY) was not an ER study…For elective surgery, it is getting traction, with 40%-50% penetration, but most people either use it 80%-90% or 10%; it's all or none, so the 'non' users have the potential to boost it."
- *Michigan:* "We are using Angiomax more because it results in less bleeding."

THE REGULATORY PERSPECTIVE

Patent foramen ovale (PFO) closure

A panel including FDA officials discussed PFO closure and the disappointing MIST-1 results of NMT Medical's StarFlex which were presented at the American Academy of Cardiology meeting in March 2006. In that trial the primary endpoint of complete elimination of migraine headaches was not achieved. Dr. Bram Zuckerman, Director of the FDA Division of Cardiovascular Devices, CDRH, said, "I guess we can call this PFO: Guilty until proven innocent."

The FDA's Dr. Andrew Farb said, "Migraine headache is serious and debilitating but not life-threatening. PFO closure requires an invasive procedure resulting in a permanent implant or change to a 'normal heart.'" He offered these comments on PFO closure for migraine:

- The rationale is based on clinical observations.
- PFOs are common incidental findings.
- The pathophysiologic mechanism is conjectural at best.
- The mechanism of benefit is not established.
- Is there durability of effect? Is there attenuation in reduced frequency of migraines over time?

He said that more databases are needed, noting, "Various theories have been proposed, such as interactive substances cross right to left or thrombolic events, but there's been no demonstration of that to date…This is what we're looking at – more data – and the data should be reliable, not just relying on the patients' recollections or physicians' recollections. We need records and diaries, and we recommend a run-in period to get a baseline from which we can compare follow-up results." He described an optimal study design:

- Randomized control.
- Efforts to maintain the blind, including a blinded headache specialist.
- Sham procedure. "The placebo responder rate is high, and the placebo response may be proportional to the 'invasiveness' of the procedure. There should be a femoral vein sheath, headphones, and shields for screens."
- Assessment of blinding post-procedure (at the end of the study), with a sensitivity analysis for impact of accidental or non-accidental unblinding of the patient.
- Efficacy endpoints:
  - Proportion of subjects with a clinically relevant reduction monthly migraine frequency vs. sham. "This must be clinically significant as well as statistically significant," he said.
  - Proportion of patients with complete migraine resolution.
  - Explore the association of migraine reduction with successful PFO closure.
- Safety endpoints:
  - Safety through 12 months.
  - Rate of major complications: mortality, stroke, cardiac tamponade, perforation, erosion, etc.

Other issues in PFO migraine studies include:

- Should subjects be included without aura?
- Should use of prophylactic medications be permitted?
- What is the definition of treatment failure – withdrawal secondary to migraine headache, increased dose or change prophylactic medications, etc.?
- How should subjects who become unblinded be handled?
- How should missing data (e.g., incomplete diaries) be handled?

There was a good deal of debate over the FDA's trial design requirements. Following are excerpts from the back and forth of the discussion.

An industry official argued that trials should be shorter than a year. He said, "When we got interested in PFOs it was from the stroke standpoint, and only since a lot of this new data came to light have we gotten interested in the migraine approach, primarily because we think it's going to be easier to prove than stroke…There are some key questions that everybody is struggling with. One is how big an issue the placebo effect is. Another is that we know a lot of patients suffer from migraine who don't have PFOs. And somewhere in these studies, we probably need to figure out if there are factors that can reliably predict which patients will benefit from PFO closure and which will not. It would save us from trying to close every PFO if it's not going to help somebody because this is a young population, and this is an implant in patients who are not suffering from a long-term problem. We have to think about putting the devices in everyone who has a

migraine headache…**I would prefer we not have a 12-month follow-up** because I think we can demonstrate efficacy in a shorter time. Tens of thousands of these devices have been implanted over the years, and, at least in experienced hands, with very low complication rates and good results, so it's not an unknown technology or unknown therapy. My preference would be a shorter follow-up of six months with some post-market surveillance. All the trials are migrating toward being very large, very long time frame, very expensive, and one concern I have is that we're going to back ourselves into a corner from an industry standpoint where only a few companies can pursue these technologies at some point. It will limit how good the technologies are, and that will affect the patient."

Dr. Farb: "We know how quickly these studies should enroll based on the perceived need to do something for these patients, so what's the right answer? The question again is one of those **balances between treatment of an otherwise normal heart**, perhaps related to migraines, perhaps not. That's what we need to get the answer to. And then there's the durability issue and placebo response. There's something about doing an invasive procedure to someone and having a response that led us to ask for longer (studies). Both groups – the sham and device group – will be on Plavix for three months and to go out to six months is just a three month difference, so by going to 12 months, we have sort of a nine month time frame. Part of the process of evaluation is to see the frequency over some period of time…It's been a difficult issue on both sides."

Dr. Bernie Meier of Switzerland, who has been a big proponent of PFO closure: "I'm disappointed that you're (the FDA is) considering complications, but you're not willing to look at the collateral beneficial effect, so if you close migraine, and it doesn't work, but it is still a possible and likely effect that the person later in life has a safe life because the PFO is closed. There may be some weeding out of people. **Why not consider a beneficial collateral effect that might happen 10 or 40 years later?**"

Dr. Farb: "It comes down to the issue of what is likely, and what kind of data we need to assess that, and what **kind of data we need to support widespread PFO closure in so many individuals**. At this point it's not enough. That type of information is helpful, but it doesn't get to the questions on the table – to be able to talk about a lifelong device looking at six months and talking about something that may occur 25 or 30 years later."

Panel moderator: "If you talk to someone who suffers from migraines, there are a lot of less-than-complete solutions that still have a huge impact on quality of life…Where is that in terms of how we define an endpoint? The long-term resiliency – the body is remarkably adaptable. Migraine isn't a one-time event, it waxes and wanes, affected by lifestyle, medications that develop tolerance, etc., so I think there are a lot of pieces here that if they were woven together, could include the other benefits in the same way we look at the other risks. If you do a blinded trial, does that mean you can't have an MRI in the sham group in the next six months? How do you defend the blind? Where are all the benefits for the use of the device? Because the other side of this, the nefarious side of this, is you sneak in the door for a migraine indication because it's easier to get. **Why not think about doing the right trial in the first place?** You have to do long-term follow-up, why not try to aggregate some of the benefit of the long-term potential of the device and think about doing the right trial?"

Dr. Farb: "We have several (trials) ready to go out of the box…Initially, I think it will be proof of principle in the studies. The justification for going on for iterations is something we do all the time…The burden will be on safety and clinical efficacy. It's hard to justify sham in that kind of setting."

Dr. Zuckerman: "You've pointed out some key factors in the post-market arena first, before we even get to maturation of this technology, so let's get back to some of your points, which are excellent. Number one is the difference between device designs. I don't think we know. Dr. Meier showed some interesting data from the first randomized migraine clinical trial. He attributed a high complication rate to operator experience. It could be device design or a host of factors. From our perspective, once we get through hoop No. 1, which is the minimum 12-month endpoint, we'd expect our initial cohort to be signed up for five-year evaluations as well as some sort of generalized **post-market experience similar to the carotid stent model**. As to how device trials could morph after we show proof of principle, I think…we'd need to consider what the control would be for an ethical trial that could show reasonable assurance of efficacy and effectiveness…**We really haven't shown proof of principle yet**, and to do so at this stage, given the placebo effect we've seen with multiple devices really requires in this experience a seldom used, but we believe necessary, trial design where we are using a sham controlled device."

FDA consultant: "In this case, the proof of principle requires the device be successful and efficient in closing the PFO and also showing a link between migraine and PFO. We have limited evidence so far, but we will have more going forward to prove the association, and so going forward with trial designs one has to consider why the trials conducted have been negative on the primary endpoint. **It may be that the wrong endpoint was chosen.** It's also possible that the hypothesis is a bit flawed, and that has to be considered going forward in choosing endpoints for a trial design."

Dr. Farb: "There are lots of patients with migraines, lots with PFOs, and some with both. **I don't think we should out of hand dismiss the total elimination of migraines as an important endpoint,** but in those patients for whom PFO is the mechanism of migraine, closing that PFO should eliminate the migraine, so I think that still shouldn't be necessarily

dismissed because the initial study wasn't met for that endpoint."

Panel moderator: "One of the things that comes to mind is a permanent implant. It takes me back to the atrial defibrillator. An **ICD doesn't cure fibrillation**; it potentially reduces embolic events, but that wasn't an endpoint. The principle indication seemed to be supported by human beings who suffered and could get up and tell powerful and consistent stories about what it was like to be at work and feel their heart go out of whack and spend the rest of the day in an emergency room, as opposed to sitting and pushing a button, feeling a zap, and going back to work. I think with (percutaneous) valves we're going to have the same kind of issue. I'm not sure that hammering everything down to hard endpoints is the place where permanent implantable devices really live; they live more in reduction of suffering. It's not a cure; it waxes and wanes, and I guess I don't feel we've got our arms around how you then measure the right endpoint in weighing the safety, the complications, of putting in an implant device. This is sort of more in the quality of life zone."

Dr. Farb: "A proportion of patients with a 50% reduction (in migraines), that would be a meaningful endpoint, so my point about resolution was more a mechanistic approach. But **patients feeling better is what we're after here**, and an acceptable proportion of patients in a trial feeling better is a very valuable and acceptable endpoint, and it doesn't have to be complete closure."

Industry representative: "In the U.S. alone, the direct cost of migraine headaches is $2.5 billion a year and indirectly it's $11.5 billion a year. **The denominator is so big that almost any improvement or lowering of that bar is going to have huge impact** if we can prove it."

Dr. Meier: "As far as a sham procedure, we've been turned down by our IRB. We cannot do a sham procedure…I don't think it's like a pacemaker or like a (percutaneous) valve that have to function the rest of the life of the patient. This closes the PFO and doesn't go away, but it doesn't have another function. It's not really the typical type of implantable device. We already have some biodegradable devices. **Why not think of this as a once-in-a-lifetime intervention** that leaves something behind but isn't necessary to function the rest of their life?"

The FDA's Dr. Julie Swain: "We have seen the placebo effect doesn't go away. As for sham controls, I have been on several IRBs, and **many think it is unethical to enroll patients in a trial with no expectation to obtain a benefit**. When you're dealing with pain, sham has a placebo effect so phenomenal that it is the only ethical way to conduct a trial. For example, many feel that nicking the skin is not a good sham for a catheter-based intervention."

Dr. Zuckerman: "How do we measure whether patients are truly feeling better?...Trial design is critical here…(And) it's critical to have the neurological community highly involved in these trials. If we were to use the PFO stroke experience as an example: Many cardiologists believe the case has been proven, but it's interesting to note that the neurological community – the American Academy of Neurology – doesn't. **To convince the agency that we have a meaningful effect will require active participation of the true experts in the migraine field**."

Panel moderator: "**We're going to need some sort of IRB education initiative** – generating wounds is not nicely perceived. If one person on the IRB gets it in their head that they don't understand why you would stab helpless human beings and put sheaths in, it could bring everything to a stop…The FDA could be helpful by providing IRBs with a statement that we understand that putting a sheath in a person to do nothing is potentially concerning to any ethics review body, but there is absolutely fundamental scientific justification for doing it here. That would provide some sort of help to sites who have tenacious IRBs. At the end of the day, it can come to a full stop at a brick wall with a sham procedure that involves any invasive element."

Biodegradable/bioabsorbable stents

Dr. Waksman said, "If vessel scaffolding is necessary only for a certain, limited time, then the permanent implant has no known advantage." He cited these advantages of absorbable stents:

- Short duration of Plavix post-stenting.
- Avoid chronic inflammatory process.
- Avoid problems of re-intervention with traditional techniques.
- Ability of vessel to perform positive remodeling.
- Peripheral application – no longer crushing issue after absorption.
- CT and MR (follow-up) compatibility.

The FDA's Dr. Jonette Foy of CDRH said, "The degradable stent could not only be a stent but a carrier…One reason this is so novel and complex for the FDA is that the vascular use is a new concern. Are there chemical interactions between stent, polymer, or drug? We need to visualize degradable stents. Can we see them on fluoroscopy? What do we do in late term follow-up? How do we find where it was placed in the patient?" As a result, she said the time course and mechanism of stent substrate or polymeric coating breakdown is critical as is the fate of degradants and the toxicity of degradants.

Dr. Foy added, "The bottom line is that the technology is far more complex when talking about degradable stents." She cited numerous challenges facing degradable stents:

- Timeline of degradation influences assessment of non-clinical and clinical study outcomes, both from a safety and efficacy standpoint.

- Correlation of *in vitro* to *in vivo* performance.
- Animal studies that consider the duration of degradation to ensure appropriate capture of late effects (often >180 days).
- Influence of degradation rate/mechanism on elution kinetics.
- Challenges with simulating the appropriate environment for engineering tests.

➢ Sterilization and stability concerns.

➢ Manufacturing consistency.

What can be done in the short-term to facilitate the advance of bioabsorbable stents? Dr. Foy suggested:

- Provide a rationale for advances and new risks of introducing a biodegradable component into the system.
- Adequately characterize the degradation profile/mechanism *in vivo*.
- Improve the ability to extrapolate data from animal models to clinical settings.
- Establish good working relationships with partners.
- Strongly encourage use of the FDA's pre-IDE program and address issues discussed in subsequent submissions.

The FDA's Dr. Robert Fiorentino (CDRH) discussed problems coming up for new bioabsorbable stent trials. He said, "Animal studies will be important in how we design the new trials. Bioabsorbable stents have entered a trial overseas, and we are actively following its progress. Key issues in new stent trials include:

➢ How new is the investigational device?

➢ Stent platform (stent material – 316L steel, CoCr, new alloys, biodegradable).

➢ Stent design (strut thickness, surface area, cell structure).

➢ The drug – whether it is a new molecule entity (NME), an approved drug but not approved for intravascular use or in a significantly different dose or concentration, or a drug already approved for a drug-eluting stent.

➢ Drug carrier/formulation – the drug release profile and manufacturing parameters.

Dr. Fiorentino added, "When we look at new products, new trials have about 2,000 subjects, both pivotal as well as registry studies. Those tend to be randomized studies. The spectrum can go down as we see interactions with existing stents – and a single-arm trial is acceptable with a historical context."

Points he told industry and investigators to consider included:

- Duration of mechanical stability, which may influence the frequency of monitoring, follow-up, and trial design.
- Develop strategies to define the target lesion after the stent has degraded – including angiographic follow.
- Potential for intravascular corrosion of the stent – including the possibility of emboli and the performance at side branches.
- Results from preclinical studies will be important in studying specific questions regarding safety.
- The safety and effectiveness of bioabsorbable stents has yet to be established.
- At least initially, bioabsorbable stent trials will be required to use an approved stent as the control.
- Randomized controlled studies for bioabsorbable coronary stent will require around 2,000 patients between the pivotal trial and a registry with the power to detect event rates around 1%.

Post-market evaluation of left ventricle assist devices (LVADs)

The FDA's Eric Chen, a team leader for VADs, described the INTERMACs data recording center, an interagency collaboration between the National Heart, Lung, and Blood Institute (NHLBI), FDA, CMS, industry, hospitals, and other clinical sites. The potential goals of INTERMACs is to:

- Facilitate the refinement of patient selection to maximize outcomes with current and new device options.
- Provide historical control data.
- Objective performance criteria (OPC).
- Develop consensus "best practice" guidelines to improve clinical management by reducing short- and long-term complications of mechanical circulatory support device (MCSD) therapy.
- Utilize MCSD Registry information to guide improvements in technology, particularly as next-generation devices evolve.

Chen described the baseline variables and endpoints for patient-device-disease profiles as baseline patient characteristics, device and implant elements, and heart failure severity variables. Discrete endpoints are death, hospitalizations, transplant, and explant for recovery. Complex endpoints are improvement indicators, adverse events, quality of life, and blood tissue parameters. Chen concluded, "For a postmarket tool, the Agency is hopeful this will provide enhanced surveillance for adverse events, device malfunctions, quality of life, and survival. It develops 'best practices' (reducing complications), provides a means for designing and conducting post-approval studies in a cost-efficient way, and allows manufacturers to obtain data from INTERMACs to fulfill postmarket requirements."

CATH LAB OF THE FUTURE

Dr. Hans Bonnier described the prototype Philips Ambient Experience room he is using at Catharina Hospital in the Netherlands. This cath lab has dynamic lighting, ceiling screens on which patients can watch lightshows, with voice-controlled images for the doctor, simple-to-use equipment, and even a scent generator to mask unpleasant smells. Dr. Bonnier said that "everything is built into the room, including echocardiography and rotoblating."

The Ambient Experience is not expected to be generally available for another two years. Dr. Bonnier said, "We developed with Philips a cath lab designed around the patient and the clinician. It is clean and efficient. It reduces anxiety and stress of the patients before, during, and after catheterization and improves the work environment of physicians and staff…It lowers the patient's average heart rate…I feel better and can do more cases."

Heather Russell RN of Fairfax Hospital described some new drugs and devices being used in the cath lab for patients in cardiogenic shock. A new trend for MI is the use of inotropes (e.g., dopamine and milrinone), which have limited potency for arrhythmias, but have a perfusion issue. She said that there is a "paradigm shift" in devices: "What we're looking at now is getting in these ventricular assist devices to help the myocardium recovery." One example she cited is the Abiomed LVAD device, which has a cannula with a motor on it and a screw, that suctions blood out of the left ventricle into the ascending aorta.

Another device that is gaining use is a circulatory support system which helps with end-organ perfusion. Russell said, "It can be LV, RV, or a bivalve assist device. It secures next to the patient's body and can get the patient through the initial hours up to 30 days. It has been trialed in 80 patients."

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